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SYNTHESIS OF THE I9-NORANALOG OF SARETT'S KETOL

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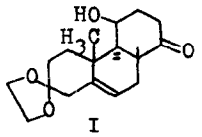
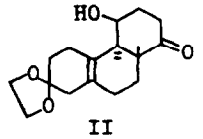
Sarett's ketol (I)[1,2] occupies a key position in the total syntheses of cortical hormones[3] in particular of aldosterone[4-7]. The present paper is concerned with synthesis of the I9-noranalog of Sarett's ketol (II) which may find application in the synthesis of I9-norcorticoids.

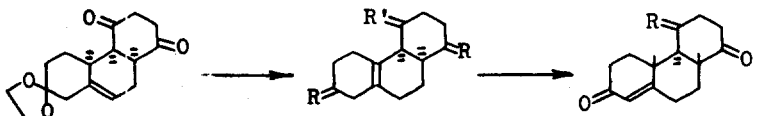


I



II

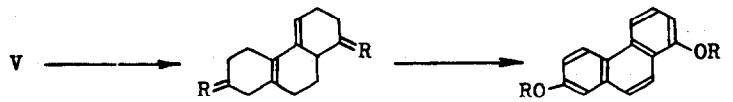
bis-Dimethylketal (IV) (m.p.[8] 84.7-86°) is obtained in good yield by refluxing the diketone (III), we have described previously[9], in a large volume of 0.5% methanolic oxalic acid solution. It proved to be quite stable to treatment with alkali, notwithstanding the β,γ-double bond and cis-fusion of the rings. Its reduction with $NaBH_4$ affords the corresponding alcohol (V), m.p. III-III.5°, which is converted to the hydroxydiketone (VI), m.p. I00.5-I0I°, by mild hydrolysis with 50% aqueous acetic acid. On treatment with KOH in aqueous methanol the hydroxydiketone VI isomerizes into the conjugated hydroxydiketone (VII), m.p. I77-I78°, λ_{max} 238 mμ (lg ε 4.I9)[I0]. The anti-trans configuration of this compound follows from the me-



III IV R=$(MeO)_2$, R'=O V R=$(MeO)_2$, R'=H,-OH VI R=O, R'=H,-OH VII R=H,-OH VIII R=O

thod of its synthesis (the thermodynamically most stable isomer) and from its oxidation (CrO_3 in acetone[II]) to the known[9] anti-trans-triketone (VIII).

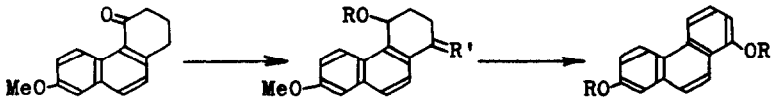
The structure of the compounds IV-VII was proved by conversion of the alcohol V into I,7-dihydroxyphenanthrene. To this end the alcohol V was dehydrated ($POCl_3+C_5H_5N$) to the diene (IX) which without purification was hydrolyzed by 50% aqueous acetic acid into the diketone (X), m.p. 123-125°, λ_{max} 237 mμ (lg ε 4.31); λ_{max}(in ethanolic KOH) in one min. after dissolution: 233,276-289(shoulder),410-420,537 mμ (lg ε 4.10, 3.65,3.60,4.03); ten min. after dissolution: 233,405-410,500-600(shoulder) mμ (lg ε 4.10,3.63,2.90); λ_{max}(after ten min. in ethanolic KOH followed by acidification with HCl; values of



IX R=$(MeO)_2$ X R=O XI R=H XIa R=Ac

lg ε are approximate) 230,330-340 mμ (lg ε 3.20,2.56); λ_{max} (in cyclohexane) 239-240 mμ. On dehydrogenation with sulfur at 240° diketone X gives I,7-dihydroxyphenanthrene (XI) as major product, isolated as the diacetate (XIa), m.p. 122.5-123.5°; λ_{max} 256,277.5,285.5,297.5,318,327,334,340,349 mμ (lg ε 4.81, 4.19,4.07,4.08,2.66,2.56,2.62,2.47,2.38).

As the described in the literature[12] synthesis of dihydroxyphenanthrene XI is highly laborious we devised another method for its preparation to obtain a sample for comparison. This method which is of interest by itself is as follows. I,2,3,4-Tetrahydro-4-oxo-7-methoxyphenanthrene (XII)[13] is reduced with $NaBH_4$ to the corresponding alcohol (XIII), m.p. II8°, λ_{max} 233.5,254.5,264,274,28I-285(shoulder),308-3I0(shoulder),322, 327 mμ (lg ε 4.85,3.62,3.74,3.76,3.56,3.00,3.3I,3.4I), acetate (XIV), m.p. I3I.5-I32°. Oxidation of the acetate XIV by CrO_3 in acetone[14] proceeds in a complicated manner, but it is possible to isolate up to 4% of desired acetoxyketone (XV), m.p. I60-I63°, λ_{max} 245,264.5,3I9 mμ (lg ε 4.5I,4.50,4.II), from

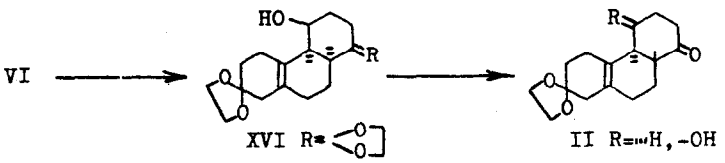


XII XIII R=H, R'=H_2 XIV R=Ac, R'=H_2 XV R=Ac, R'=O XI R=H XIa R=Ac

the resulting mixture by means of chromatography. On refluxing with $C_5H_5N.HCl$ the acetoxyketone XV straightforwardly gives I,7-dihydroxyphenanthrene (XI), m.p. I96.5-I98.5°, λ_{max} 235.5, 253-255(shoulder),267,3I2,328,343,360 mμ (lg ε 4.36,4.42,4.52, 3.79,3.I8,3.30,3.33); the diacetate (XIa) proved to be identical with that described above.

Since the compounds IV-VI have no selective absorption of high-intensity above 220 mμ and their NMR spectra[15] show no vinyl proton signals the double bond is located in the position shown.

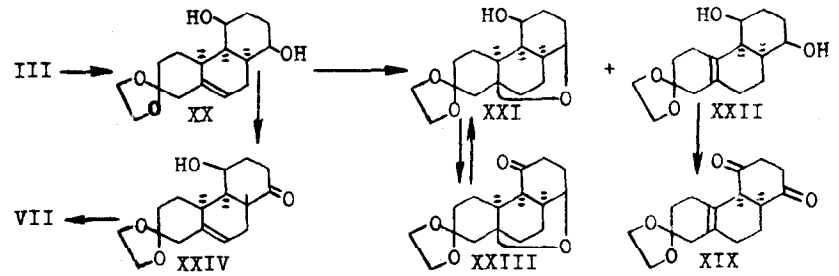
Ketalisation of the hydroxydiketone VI by ethylene glycol in the presence of adipic acid[16] gives rise largely to the di-



XVII R=O XVIII R=O

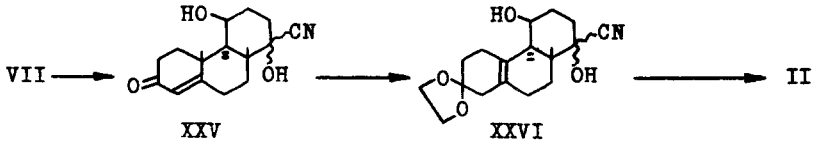
ketal (XVI), m.p. I22.2-I22.7°, and to minor amounts of the cis-hydroxyketone (XVII) (not obtained in pure state). The latter isomerizes (in aqueous-methanolic KOH) to the trans-hydroxyketone II, m.p. I22-I23°; the trans fusion being shown by oxidation to the trans-diketone (XVIII), m.p. I42-I43°, differing from the cis-diketone (XIX) described below. These reactions at the same time indicate cis fusion of the rings in compounds IV-VI, XVI and XVII.

The β-configuration of the hydroxyl group in the hydroxyketone II (which is essential for its use in the synthesis of I9-norcorticoids) follows from the related hydroxydiketone VII, which is synthesized, although by a more complicated route, yet such that it proves the β-configuration of the hydroxyl group in the compound. Reduction of diketone III by $LiAlH_4$ in tetrahydrofuran solution is stereoselective giving the diol (XX), m.p. I08-I09° or 90-I00° (dihydrate). On treatment with TsOH. H_2O diol XX isomerizes to a mixture of the oxidoalcohol (XXI), m.p. 93-I05° (hydrate) (the proof of whose structure will be



published elsewhere), and the diol (XXII), m.p. 142-143°, no vinyl proton peaks in the NMR spectrum. Oxidation of the diol XXII (CrO_3 in acetone[11]) leads to the cis-diketone XIX, m.p. 123.5-124.5°, which shows no selective high-intensity absorption above 220 m . The formation of the oxidoalcohol XXI and its reconversion by reduction of the corresponding ketone (XXIII), m.p. 132.8-133.8°, with sodium in ethanol and liquid ammonia[17] gives an unambiguous proof of the configuration of diol XX. Oppenauer oxidation[2] of the diol XX gives in moderate yield the syn-trans-hydroxyketone (XXIV), m.p. 139.5-140.5°. After removal of the ketal protection by means of perchloric acid in tetrahydrofuran the hydroxyketone XXIV gives rise to the hydroxydiketone VII (with inversion at C_{4b}).

For preparative purposes it is more better to synthesize the hydroxyketone II by a route which, although longer, gives better yields. Treatment of the hydroxydiketone VII with acetonecyanohydrin in the presence of triethylamine[18] leads to selective cyanohydrination of the saturated keto group to give the monocyanohydrin (XXV), m.p. 171-171.5° (with decomp.). Ke-



talisation of the hydroxyketocyanohydrin XXV with ethylene glycol in the presence of $TsOH.H_2O$ and traces of acetonecyanohydrin[19] gives the ketal (XXVI) (not isolated) which splits off hydrocyanic acid on heating with pyridine to form the hydroxyketone II.

The over-all yield of hydroxyketone II along the scheme III→IV→V→VI→VII→XXV→XXVI→II (without isolation of hydroxydiketone VI) reaches 20%.

Identification and purity tests of the products and analyses of the reaction mixtures were carried out by means of binderless thin layer chromatography on alumina or silica gel[20].

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